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Potentially inappropriate medication: prevalence, risk of hospitalisation and associated healthcare costs in the general older population of Switzerland

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Summary

BACKGROUND: Potentially inappropriate medications (PIM) and their public health burden in the general older population in Switzerland remain largely unexplored. The aim of this study was to estimate the PIM prevalence and the association between the exposure to PIMs and the time to hospitalisation after PIMs as well as the total healthcare costs in the general older population of Switzerland.

METHODS: We performed an observational retrospective study using health insurance claims data from patients aged 65 years or older. PIMs were defined based on the Beers criteria and the PRISCUS list. A repeated cross-sectional design was used to assess PIM prevalence, defined as the proportion of patients with PIM prescription. In a separate matched case-control design, a time-dependent multiple Cox proportional hazards regression was applied to examine the association between PIM prescription and time to first hospitalisation. To examine the association between the exposure to PIM and healthcare costs, a negative binomial regression model was used.

RESULTS: In 2022, one-third of the population aged 65 years or older was prescribed at least one PIM. The highest risk of hospitalisation occurred within the first 15 days after the initial PIM prescription (hazard ratio [HR]: 2.72, 95% confidence interval [2.25–3.27]) and gradually decreased over time (after 30 days: HR: 2.16 [1.75–2.66]. 60 days: HR: 1.76 [1.50–2.05]. 90 days: HR: 1.67 [1.42–2.97]. 180 days: HR: 1.50 [1.37–1.66]. 365 days: HR: 1.34 [1.25–1.44]). Patients with PIM prescription showed on average CHF 3194 [3047.67–3341.10] higher costs than patients without PIM.

CONCLUSION: This study showed a high PIM prevalence and associated public health burden in terms of hospitalisations and healthcare costs in the general older population of Switzerland. Our findings may indicate limited awareness in prescribing PIMs in primary care and the challenge associated with managing conflicting therapeutic recommendations in vulnerable patients. Given the ageing population and rising healthcare costs, the study highlights the urgent need for targeted strategies to reduce PIMs.

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Introduction

Potentially inappropriate medications (PIM) are described as medications that should be avoided due to their high risk of adverse events and lack of evidence of effectiveness [1]. The impact of PIMs on various outcomes such as healthcare utilisation and costs has been widely studied. PIM use was associated with increased healthcare utilisation [2, 3], risk of all-cause [4–7], drug-related [8–10] and fall-related hospitalisations [3, 11, 12]. PIM exposure was also associated with emergency [10] and general practitioner (GP) [11] visits as well as higher healthcare costs in general [2, 3, 13, 14]. Consequently, PIMs pose a significant challenge for high-quality and efficient healthcare systems.

PIMs are of particular relevance in elderly healthcare since older adults are at greater risk of adverse drug events for a number of reasons. First, age-related changes in pharmacokinetics and pharmacodynamics increase drug sensitivity and the risk of adverse events [15]. Second, despite

being the primary consumers of prescribed drugs [16], older adults are often underrepresented in clinical trials, leading to a lack of robust evidence on the safety and efficacy of medications for this population [17]. Finally, the high prevalence of chronic illnesses among older adults, which requires complex drug regimens, increases the risk of adverse drug-drug interactions. Considering these challenges, various screening tools to identify and reduce PIMs in older patients have been developed and published. The Beers criteria from the US were the first comprehensive measure introduced and many countries have since adapted or developed similar criteria to suit their specific pharmaceutical markets and treatment practices, such as the PRISCUS list in Germany [18] or the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) in Ireland [19].

In Switzerland, up-to-date studies on PIMs and their implications for the general older population are scarce, despite the country's ageing population and rising healthcare costs [20, 21]. While recent studies have examined the prescribing prevalence in specific settings, such as nursing homes [22], general practice [23] or specific health insurance schemes [24], there is no current prevalence estimate of PIM prescribing that can be generalised to the total population of Switzerland. Previous research [25] examined the association between PIM prescription and hospitalisation based on data from 2016, but assessed the exposure to PIM and the subsequent hospitalisation annually, without considering the exact time to event. This approach lacked capture of the temporal relationship between exposure and outcome, and thus may have led to an underestimation of short-term effects of the potential harm of PIMs. Another study [12], which examined the risk of hospitalisation following an initial PIM prescription, was based on outdated data (2008 to 2012) and the results were not generalisable to the total Swiss population since the analyses focused on managed care insurance models. Therefore, our study aimed to address the following two primary objectives: (1) To assess current data on PIM prevalence, including population-based time trends, and (2) to evaluate the association between the exposure to PIM and (a) the time to first all-cause hospitalisation as well as (b) the total healthcare costs in the general older population of Switzerland.

Methods

Data

This observational retrospective study was based on routine claims data from one of the largest health insurance companies in Switzerland (Helsana Group). The data contained anonymised patient-level information, covering drugs (substance and dosage), medical services (in- and outpatient), laboratory tests, chosen health insurance plan, deductible level and sociodemographic information such as age, sex and living area.

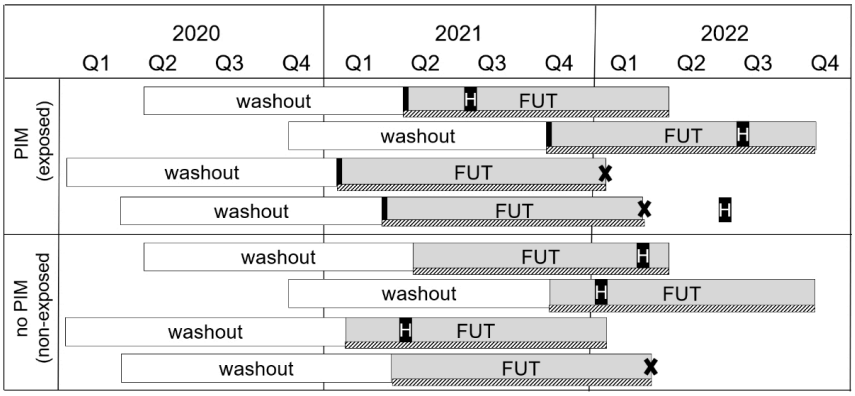
Study design and study sample

The analysis of PIMs in the general older population consisted of two parts:

- **Prevalence analysis:** To assess PIM prevalence from 2012 to 2022, a repeated cross-sectional design was used. The study population included patients aged 65 years or older with at least one prescription of any drug per year.
- **Outcome analysis:** To examine the association between the prescription of PIMs (exposed/non-exposed) and 2a) time to first all-cause hospitalisation as well as 2b) total healthcare costs, a matched case-control design (figure 1) was applied. The two outcome variables – (i) time to hospitalisation (date of PIM prescription to admission date of first hospitalisation after PIM prescription) and (ii) total healthcare costs (sum) – were evaluated within 365 days following the first PIM prescription in 2021. The follow-up period was censored at 365 days if hospitalisation did not occur.

Figure 1. : Study design on PIM prescriptions and associated hospitalisation and healthcare costs.

Abbreviations: FUT, follow-up time of 365 days; PIM, potentially inappropriate medication.



The study sample included patients aged 65 years or older with continuous insurance coverage between 2020 and 2022. Patients with at least one PIM prescription between 1 January 2021 and 31 December 2021 were classified into the exposed group, whereas the non-exposed group included patients without a PIM prescription during the same time period. For patients in the exposed group, the start of the follow-up period was defined by the date of the initial PIM prescription (index date). For all patients in the non-exposed group, 12 data entries were generated, with a notional index date on the first day of each month from January to December (hereafter referred to as patient-months), which determined their starting date of the follow-up period (figure 2). The combination of month and year of the index dates served as a matching variable in the propensity score procedure, and ultimately served to account for potential seasonal effects.

Figure 2. : Generation of additional entries for each control in the dataset.

Abbreviations: PIM: potentially inappropriate medication.

Notes: All numbers depicted are for illustration. The patient ID in combination with the index date represents the unique identifier.

patient ID	PIM	index date
1	1	20.01.2021
2	0	-

patient ID	PIM	index date
1	1	20.01.2021
2	0	01.01.2021
2	0	01.02.2021
2	0	01.03.2021
2	0	01.12.2021

From both the exposed and non-exposed group, patients who received at least one PIM prescription and/or were hospitalised during the 12-month period before the corresponding index date were excluded. We applied this washout period to eliminate any potential unobserved effects from

prescriptions and hospitalisations prior to the index date. In addition, from the non-exposed group, we excluded patient-months in which at least one PIM prescription was recorded 12 months after the notional index date (which can be up to 2022) and in which no drug at all was recorded in the 12-month period before and/or after the corresponding index date.

PIM definition and assessment

We defined PIMs based on the Beers criteria [26] and the PRISCUS list [18]. Other validated criteria such as the STOPP criteria [19] could not be considered for the analyses, because they are based on diagnoses, which are not included in our claims database. The identification of PIMs was based on the Anatomical Therapeutic Chemical (ATC) classification system by the WHO [27], with additional specifications considering number of prescribed packages, package size, dosage, mode of administration (e.g. oral, topical, parenteral) and combinations of specific ATCs with package levels defined based on the Swiss Pharmacode. The analysis considered only drugs that were licensed and listed for reimbursement in Switzerland. The drug classes that include PIMs are presented in table S1 in the appendix. For the assessment of PIM prevalence from 2012 to 2022, we used the year-specific versions of the two PIM lists. The analysis of the association with hospitalisation and healthcare costs was based on the Beers 2019 criteria [26] and the PRISCUS 1.0 list [18].

For the analysis, a total of 126 active agents (unique ATC codes) and combinations were included as PIMs. Among these, 37% from the 2019 Beers criteria (62 of a total of 168) and 77% from the PRISCUS list (64 of a total of 83) were licensed in Switzerland and covered by the mandatory health insurance scheme.

Outcomes

The outcomes of interest were (2a) time to first all-cause hospitalisation after the initial PIM prescription in 2021 and (2b) total healthcare costs, both evaluated during the 1-year follow-up period. Hospitalisation was defined as an inpatient stay (≥1 night) in an acute care hospital. Total healthcare costs were defined as the sum of in- and outpatient care costs per patient and year. Outpatient costs included physician visits both from GPs and specialists, medications, laboratory tests, outpatient visits to hospitals, paramedical visits, nursing and medical equipment. Inpatient costs included the cost of hospitalisation in acute care, psychiatric and rehabilitation hospitals, nursing homes, emergency transport services, and related costs for medications, laboratory tests and medical equipment.

Covariables

Patients' sociodemographic, health insurance and morbidity characteristics were used as matching variables and covariates. Sociodemographic and health insurance characteristics were assessed at the time point of the (notional) index date whereas morbidity characteristics were assessed based on the year prior to the index date (same time period as washout). Covariates for sociodemographic and health insurance characteristics included age, sex, language region, area of living (urban-rural typology), chosen health insurance model and deductible level. Age was analysed as a continuous variable, and sex as male or female. Language region distinguished the German-, French- and Italian-speaking parts of Switzerland. Area of living was categorised as urban, intermediate or rural. The health insurance model included the standard care model (SCM) and integrated care health insurance models with varying levels of integrated care: family doctor model (FDM), FDM-light, telemedicine model (TM), with FDM representing the highest degree of integrated care. Deductible level was categorised as low or high. Covariates of morbidity included number of physician visits, consulted physicians, unique ATCs and chronic diseases, as well as outpatient and inpatient costs and inpatient stay in a nursing home. The number of physician visits and consulted physicians included both primary care and specialist contacts. Chronic diseases were identified using pharmaceutical cost groups (PCGs) because medical diagnoses are missing from the given claims dataset. PCGs are a well-established and frequently applied pharmaceutical classification to assess morbidity based on patients' prescribed medication when clinical data are not available [28].The number of chronic diseases was categorised as 0, 1–3, 4–5 or ≥6 chronic conditions. Outpatient and inpatient costs encompassed the same cost categories as described in the outcome section. An inpatient stay in a nursing home was defined as a stay (≥1 night) in such a facility.

Statistical analysis

To assess the PIM prevalence from 2012 to 2022, we calculated the proportion of patients who received at least one PIM prescription for each year. PIM exposure was assessed per quarter and aggregated at the annual level (binary coded: exposed/non-exposed). Multiple prescriptions of PIMs were not explicitly considered, but simply classified as exposed.

We used descriptive statistics to summarise patient and outcome characteristics of the study sample used for the outcome analysis. Counts and percentages were used for categorical variables; means and standard deviations for continuous variables.

To balance the differences in baseline characteristics between patients in the exposed and non-exposed group of the study sample, we conducted 1:1 nearest neighbour matching with exact matching on categorical covariates including index date (month-year level), sex, language region, area of living, health insurance model, deductible level, number of PCGs and inpatient stay in a nursing home. The variables age, healthcare costs, as well as the number of unique ATCs, outpatient visits and consulted physicians were further used for the nearest neighbour matching. To evaluate the comparability between the two groups, we calculated the summary statistics for baseline characteristics of the covariates and the density distributions of the propensity scores before and after propensity score matching (PSM), the standardised mean differences as well as the variance ratios, and the density distributions for each variable in the matched case and control groups.

Based on the matched data, we applied a multiple Cox proportional hazards (CPH) model and calculated time-dependent adjusted hazard ratios (HR) to test for the association between PIM/no PIM prescription and the time to first hospitalisation. Given that the proportional hazards (PH) assumption for the predictor of interest (PIM/no PIM, exposed vs non-exposed) was not satisfied (statistical test and graphical diagnostic shown in table S2 and figure S3 in the appendix), time-dependent adjusted HRs were calculated using a step function. A step function is a simple approach to model time-varying coefficients when the PH assumption is violated. It divides the sample into several time intervals and stratifies a CPH model according to the defined time intervals [29, 30], in this case 1–15 days, 15–30 days, 30–60 days, 60–180 days and greater than 180 days. For the association between the exposure to PIM and total healthcare costs, we calculated a negative binomial regression model, and based thereon, the marginal effects (ME) at the mean for better interpretability of the effects.

To assess the sensitivity of the regression analysis, we performed several sensitivity analyses. First, to minimise reverse causality, we excluded patients hospitalised within the first 15 days of follow-up, as hospitalisations in this period may reflect pre-existing conditions that lead to PIM prescription rather than PIM effects. Second, we excluded patients aged 80 years or older [31] as their PIM use is likely to be unavoidable due to lack of alternative treatments associated with their advanced age. Third, to account for potential bias due to multiple entries from the same person in the control group (12 vs 1), we used a subsample that included only distinct matches of non-exposed (no PIM), so that each patient occurred only once in the dataset.

For all analyses, the R programming language, version 4.1.0 (R Foundation for Statistical Computing), was used. The s*urvival* package [32] was used for the CPH model, and the MEs at the means were calculated using the *mfx* package [33].

Ethics approval and informed consent

For the analysis, we used retrospective, pre-existing and anonymised administrative healthcare claims data. The authors had no access to information that could identify individual patients during or after data collection. According to the Swiss Federal Act on Research involving Human Beings (Human Research Act, HRA) [34] and the local ethics committee of the canton of Zurich, ethical approval and patients' informed consent are not required for this type of study. The data were accessed on 14 June 2024 for the research purposes.

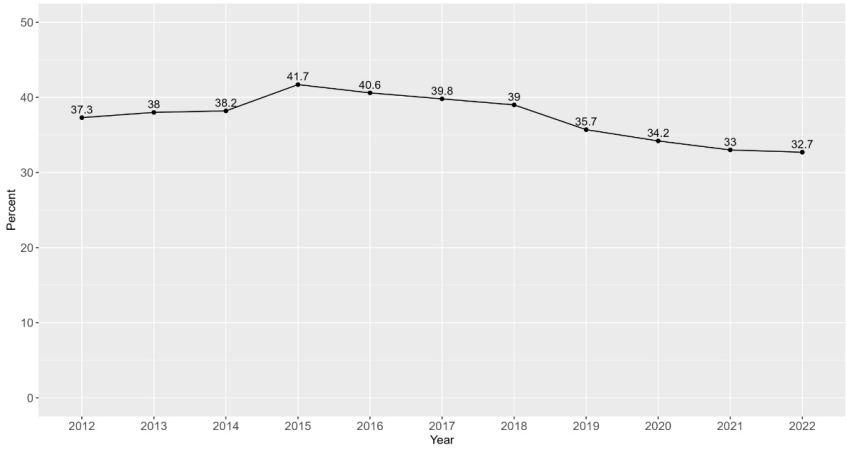
Results

PIM prevalence over time

The prevalence analysis was based on annual samples that ranged from 251,484 patients aged 65 years or older in 2012 to 272,058 patients in 2022. Figure 3 shows the 1-year PIM prevalence in the general older population from 2012 to 2022. In 2022, around one-third of patients were prescribed at least one PIM. The prevalence generally decreased over the last decade with a modest increase

from 37% in 2012 to 42% in 2015. After 2015, the PIM prevalence gradually decreased by a total of approximately 10%-points until 2022 (figure 3). Detailed annual prevalences are presented in table S4 in the appendix.

Figure 3. : Prevalence of potentially inappropriate medications over time.



Study population of the outcome analysis

Figure 4 presents the flowchart of the selected study sample used for the outcome analysis. A total of 299,847 patients aged 65 years or older were included for the analysis. After applying the exclusion criteria of non-continuous insurance coverage, the sample comprised 159,594 patients in the non-exposed group (no PIM) and 78,057 in the exposed group (PIM). The inclusion of 12 notional index dates, the dataset of the non-exposed group resulted in 1,915,128 entries ("patient-months"). Following additional exclusion criteria (e.g. washout period) for both the exposed and the non-exposed group, the sample comprised 123,330 patients in the non-exposed group and 17,738 in the exposed group. After PSM between those two groups, the final sample included 17,700 matched pairs, resulting in a total of 35,400 patient (-months). Notably, within the exposed group, 47% of the patients showed multiple PIM exposures within one year following the initial exposure.

Figure 4. : Flowchart of the selected study sample (outcome analysis).

Abbreviations: Ne: number of entries; Np: number of unique patients.

Notes: number of entries refers to patient-months (notional index date at beginning of each month), which might come from the same patient in the non-exposed group.

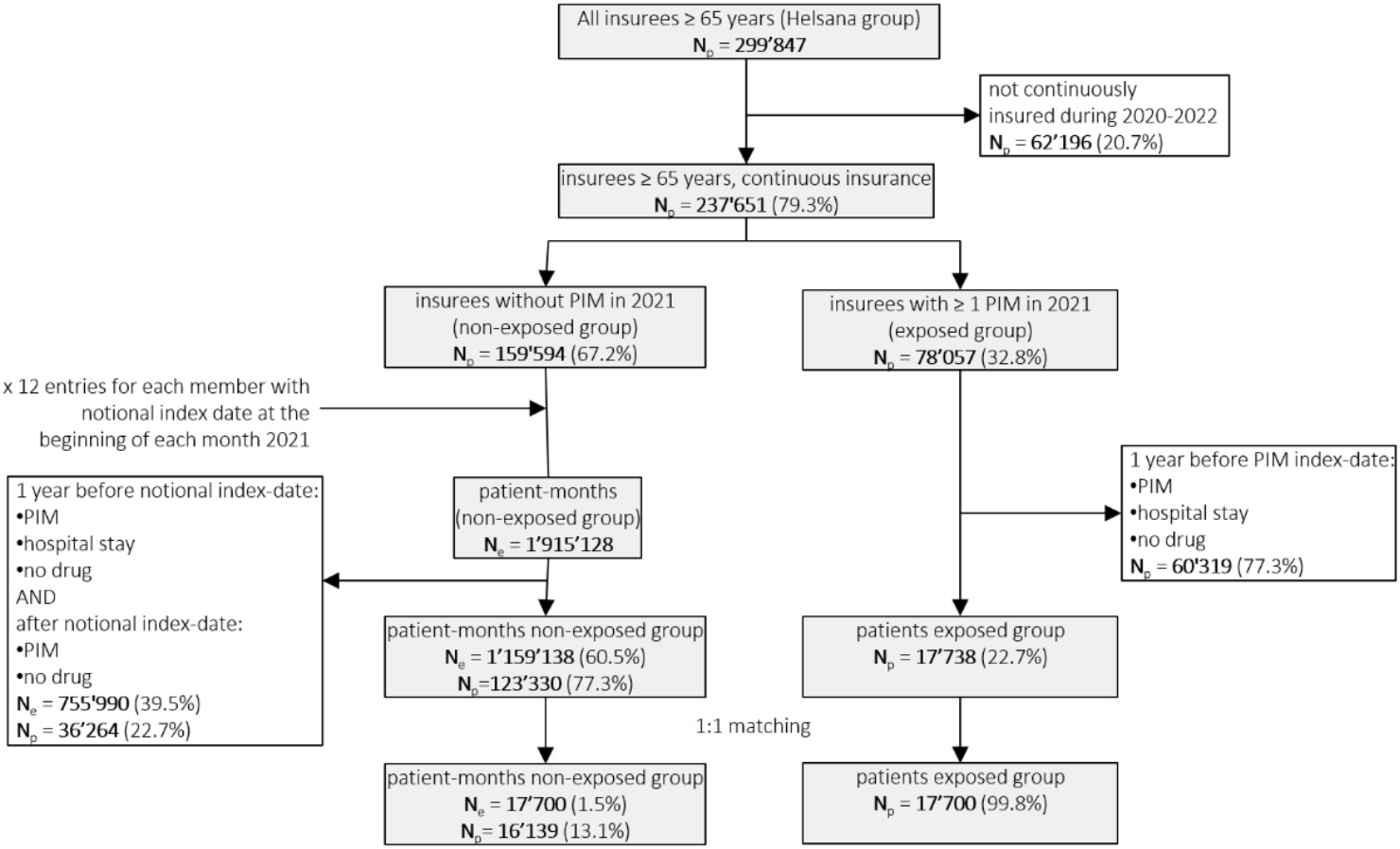


Table 1 presents the baseline characteristics of the study population after applying PSM, showing evenly distributed covariates between patients with and without PIMs. In both groups, 6 of 10 patients were women, and the average is about 76 years. Most patients resided in urban areas and in the German-speaking part of Switzerland. Almost 40% of the patients chose a SCM and 90% a low deductible level. Around 90% of the patients had at least one chronic condition, had on average around 14 physician visits from two different physicians and received 11 different ATCs in the year before the index date. Only 4% of patients were in a nursing home during the washout period, of whom 70–80% in each group were in a nursing home for the entire year during the washout period. The average outpatient / inpatient cost per patient in the year before the index date was approximately CHF 5800 / CHF 700 (comprising costs for inpatient stays in nursing homes, rehabilitation and psychiatric clinics, excluding all acute hospitalisation costs). The standardised mean differences, variance ratios and density distributions of each variable, as well as the density distributions of propensity scores showing common support between the two groups, are presented in figure S5, table S6, figure S7 and figure S8 in the appendix. The baseline characteristics of the covariates prior to PSM are shown in table S9 in the appendix.

Table 1. : Baseline characteristics of the matched study population (outcome analysis).

Variables			Total	No PIM (non-exposed)	PIM (exposed)
Study population		n (%)	35,400 (100%)	17,700 (50.0%)	17,700 (50.0%)
Female sex		n (%)	22,058 (62.3%)	11,029 (62.3%)	11,029 (62.3%)
Age		mean (SD)	76 (7.2)	76 (7.2)	76 (7.1)
Living area	Urban	n (%)	23,564 (66.6%)	11,782 (66.6%)	11,782 (66.6%)
	Rural	n (%)	4562 (12.9%)	2281 (12.9%)	2281 (12.9%)
	Intermediate	n (%)	7274 (20.5%)	3637 (20.5%)	3637 (20.5%)
Language region	German-speaking	n (%)	26,768 (75.6%)	13,384 (75.6%)	13,384 (75.6%)
	French-speaking	n (%)	5282 (14.9%)	2641 (14.9%)	2641 (14.9%)
	Italian-speaking	n (%)	3350 (9.5%)	1675 (9.5%)	1675 (9.5%)
Health insurance plan	SCM	n (%)	13,894 (39.2%)	6947 (39.2%)	6947 (39.2%)
	FDM	n (%)	13,174 (37.2%)	6587 (37.2%)	6587 (37.2%)
	FDM-light	n (%)	4248 (12.0%)	2124 (12.0%)	2124 (12.0%)
	TM	n (%)	4084 (11.5%)	2042 (11.5%)	2042 (11.5%)
Deductible: CHF ≤500		n (%)	31,826 (89.9%)	15,913 (89.9%)	15,913 (89.9%)
Number of chronic conditions (wo)	0	n (%)	4100 (11.6%)	2050 (11.6%)	2050 (11.6%)
	1–3	n (%)	22,200 (62.7%)	11,100 (62.7%)	11,100 (62.7%)
	4–5	n (%)	7010 (19.8%)	3505 (19.8%)	3505 (19.8%)
	≥6	n (%)	2090 (5.9%)	1045 (5.9%)	1045 (5.9%)
Nursing home (wo)		n (%)	1436 (4.1%)	718 (4.1%)	718 (4.1%)
Outpatient consultations		mean (SD)	14 (12.4)	13 (12.7)	14 (12.0)
Different physicians (wo)		mean (SD)	2 (1.6)	2 (1.6)	2 (1.6)
Unique ATCs (wo)		mean (SD)	11 (6.7)	11 (6.6)	11 (6.7)
Costs in CHF (wo)	Outpatient costs	mean (SD)	5800 (7896.7)	5731 (7385.6)	5868 (8376.3)
	Inpatient costs	mean (SD)	719 (4131.5)	716 (4032.7)	723 (4149.4)

Abbreviations: FDM: family doctor model; PIM: potentially inappropriate medication; SCM: standard care model; SD: standard deviation; TM: telemedicine model; wo: washout. Notes: Washout refers to the period one year prior to the corresponding index date. Outpatient consultations include primary care and specialist physicians. Inpatient costs include costs for inpatient stays in nursing homes, rehabilitation and psychiatric clinics. FDM: The treating physician is part of a physician network, which has a cooperation agreement with the health insurance, which defines reimbursement for integrated care services and regulates the type of cooperation and commits to a network-specific quality standard. FDM-light: In contrast to FDM, the treating physician is not part of an approved physician network. Nursing home was defined as a ≥1 overnight stay.

Table 2 presents the descriptive comparison of the outcome variables including all-cause hospitalisation (yes, no), time to first hospitalisation among hospitalised patients and total healthcare costs. Approximately 23% of the patients in the exposed and 16% in the non-exposed group were hospitalised in the year following the PIM or during the index year. Patients who were prescribed PIMs were generally hospitalised earlier and had higher total healthcare costs than those without PIM prescriptions.

Table 2: Outcome characteristics of the study population (outcome analysis).

Outcome		Total	No PIM (non-exposed)	PIM (exposed)
Hospitalisation	n (%)	6919 (19.5%)	2785 (15.7%)	4134 (23.4%)
Days until first hospitalisation	mean (SD)	162 (108.0)	175 (106.3)	153 (109.0)
Total healthcare costs	mean (SD)	CHF 9897 (CHF 13,779.5)	CHF 8280 (CHF 11,446.6)	CHF 11,515 (CHF 15,604.5)

Abbreviations: n: number; SD: standard deviation.

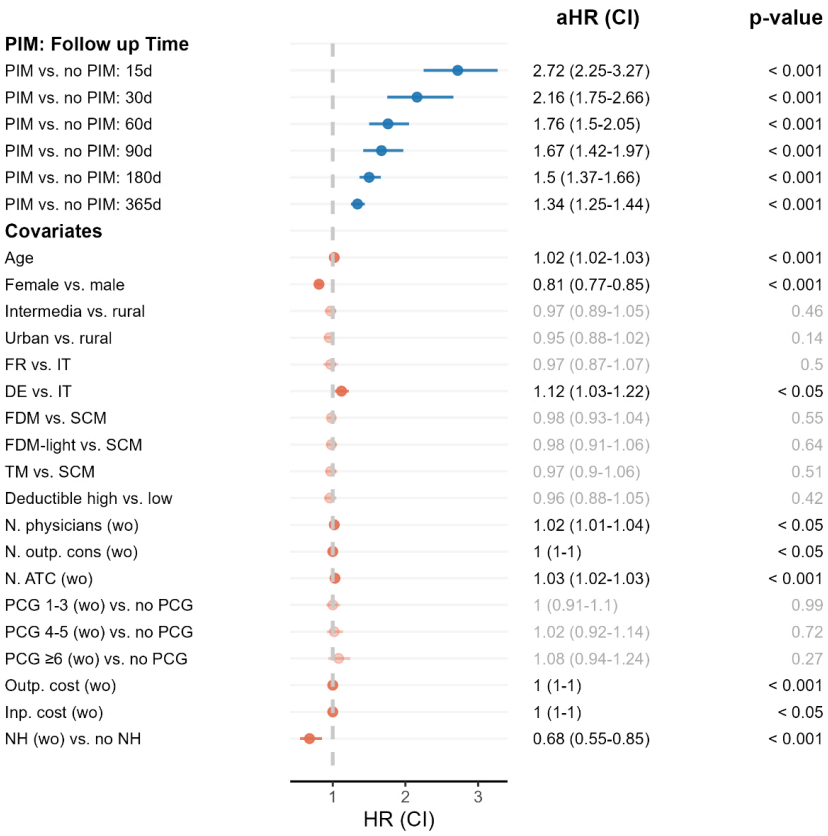
PIM and time to all-cause hospitalisation

Figure 4 shows the estimated HR from the CPH model, representing the association between patients with exposure to PIM and time to first hospitalisation. The CPH model revealed a significant association between PIM exposure and an increased risk of hospitalisations. The highest risk of hospitalisation occurred within the first 15 days after the initial PIM prescription (HR: 2.72, 95% CI:

[2.25–3.27]) and gradually decreased over time (after 30 days: HR: 2.16 [1.75–2.66]. 60 days: HR: 1.76 [1.50–2.05]. 90 days: HR: 1.67 [1.42–2.97]. 180 days: HR: 1.50 [1.37–1.66]. 365 days: HR: 1.34 [1.25–1.44]). Increased risk of hospitalisation was also observed in patients who were older (HR: 1.02 [1.02–1.03]) and lived in the German-speaking part of Switzerland (HR: 1.12 [1.03–1.22]). For patient's morbidity characteristics, the number of outpatient visits (HR: 1.00 [1.00–1.00]), consulted physicians (HR: 1.02 [1.01–1.04]) and the number of unique ATCs (HR: 1.03 [1.02–1.03]), as well as the healthcare costs (both out- and inpatient: HR: 1.00 [1.00–1.00]) were associated with a higher risk of hospitalisation. Being female (HR: 0.81 [0.77–0.85]) and living in a nursing home (HR: 0.68 [0.55–0.85]) were associated with a lower risk of hospitalisation.

The sensitivity analysis showed comparable results for the coefficients of PIM vs no PIM, both when excluding patients hospitalised within the first 15 days of follow-up (subsample of 17,290 matched patients) and patients aged 80 years and older (subsample of 12,934 matched patients). Furthermore, the results remained stable when a subsample of 16,139 distinct matches of exposed and non-exposed patients was used. The full results of the sensitivity analysis are presented in tables S10, S11 and S12 in the appendix.

Figure 5. : Estimated association between PIM exposure and hospitalisation based on a CPH model. Abbreviations: aHR: adjusted hazard ratio; ATC: Anatomical Therapeutic Chemical (classification system); CI: confidence interval; d: days; DE: German-speaking area; FDM: family doctor model; FR: French-speaking area; inp.: inpatient; n: number; NH: nursing home stay; outp.: outpatient; PCG: pharmaceutical cost group; PIM: potentially inappropriate medication; SCM: standard care model; TM: telemedicine model; wo: washout. Notes: Sample size: 35,400 (17,700 matched pairs). Washout refers to the period one year prior to the corresponding index date. The high deductible level is CHF ≥500. Outpatient consultations and number of physicians include primary care and specialist physicians. Inpatient costs include costs for inpatient stays in nursing homes, rehabilitation and psychiatric clinics. FDM: The treating physician is part of a physician network, which has a cooperation agreement with the health insurance, which defines reimbursement for integrated care services and regulates the type of cooperation and commits to a network-specific quality standard. FDM-light: In contrast to FDM, the treating physician is not part of an approved physician network.

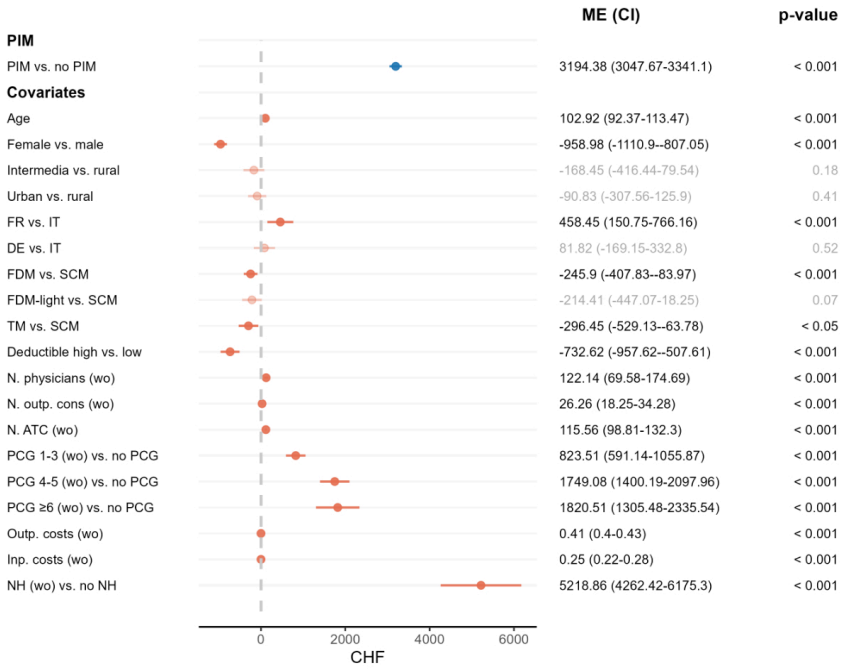


PIM and total healthcare costs

Figure 5 presents the estimated ME from the negative binomial regression model, representing the association between patients exposed to PIM and total healthcare costs. Patients with at least one PIM prescription showed on average CHF 3194 higher costs than patients without PIM (ME: 3194.38 [3047.67–3341.10]). Patient age (ME: 102.92 [92.37–113.47]), living in the French-speaking part of Switzerland (ME: 458.45 [150.75–766.16]) as well as patient's morbidity characteristics were also associated with higher healthcare costs (ranging from inpatient costs: ME: 0.25 [0.22–0.28] to nursing home stay: ME: 5218.86 [4262.42–6175.30]). In contrast, being female (ME: -958.98 [-1110.90–-807.05]), enrolment in a FDM (ME: -245.90 [-407.83–-83.97]) or a TM (ME: -296.45 [-529.13–-63.78]) and a higher deductible level (ME: -732.62 [-957.62–-507.61]) were associated with lower healthcare costs. The estimated IRRs are presented in table S13 in the appendix.

The sensitivity analysis showed robust results. The coefficients of PIM vs no PIM were comparable to those from the main sample, when excluding patients hospitalised within the first 15 days of follow-up and patients aged 80 years. Using a subsample of distinct matches of exposed and non-exposed patients did not notably alter the results. The full results of the sensitivity analysis are presented in tables S10, S11 and S12 in the appendix.

Figure 6. : Estimated association between the prescription of PIMs and total healthcare costs in the follow-up period. Abbreviations: ATC: Anatomical Therapeutic Chemical (classification system); CI: confidence interval; d: day; DE: German-speaking area; FDM: family doctor model; FR: French-speaking area; inp.: inpatient; ME: marginal effects; n, number; NH: nursing home stay; outp.: outpatient; PCG: pharmaceutical cost group; PIM: potentially inappropriate medication; SCM: standard care model; TM: telemedicine model; wo: washout. Notes: Sample size: 35,400 (17,700 matched pairs). Washout refers to the period one year prior to the corresponding index date. The high deductible level is CHF ≥500. Outpatient consultations and number of physicians include primary care and specialist physicians. Inpatient costs include costs for inpatient stays in nursing homes, rehabilitation and psychiatric clinics. FDM: The treating physician is part of a physician network, which has a cooperation agreement with the health insurance, which defines reimbursement for integrated care services and regulates the type of cooperation and commits to a network-specific quality standard. FDM-light: In contrast to FDM, the treating physician is not part of an approved physician network.



Discussion

Our study revealed a high PIM prevalence in the general Swiss older population, despite a gradual decrease over the last decade. It further showed a strong association between exposure to PIM and time to all-cause hospitalisation as well as increased total healthcare costs in the follow-up period.

The estimated PIM prevalence (33% in 2022) is in line with findings from previous studies from other European countries. Brick et al. systematically reviewed the PIM prevalence in older adults residing in Central and Eastern Europe in all care settings up to 2019 and showed a PIM prevalence of 34.6% [35]. In another systematic review, Tian et al. assessed the PIM prevalence among older adults worldwide from 1990 to 2022 and reported a pooled prevalence of 35% for Europe [36]. Both the national and international high PIM prevalence are surprising, since the concept of PIM was formally introduced in the early 1990s in the US and since then numerous assessment tools have been continuously developed and adapted across various countries around the world to prevent PIMs. We assume that one reason for the high prevalence is still a lack of knowledge of PIM and PIM assessment tools among healthcare providers, as suggested by studies [37, 38]. There might also be clinical reasons based on the patient's individual health status. Older adults are affected by age-related physiological changes and are more likely to have chronic conditions requiring multiple medications. Managing complex patient cases can challenge healthcare providers in balancing effective and safe medication which might increase the risk of PIM exposure. For some patients, PIM may be unavoidable despite best efforts, where no other prescription options are available to reduce disease progression or mitigate pain.

Nevertheless, a decline in PIM prevalence has been observed over time in Switzerland and in Germany [39]. This development could be attributed to several factors. First, the introduction of newly updated PIM lists and their distribution might have gradually raised awareness of PIMs among healthcare providers and led to a more considered prescribing practice over the last decade. Second, the increased use of software programs developed to detect inappropriate medications likely played a role in preventing PIM prescriptions [40]. Third, the implementation of chronic care programmes and innovative integrated care models might have indirectly contributed to the reduction of PIMs by improving the overall care of chronic conditions, which are highly prevalent in older adults and often mean multiple medications per patient.

For the association between patients with PIM prescription and hospitalisation, the study found a significantly higher risk of hospitalisation in patients who received PIM prescriptions compared to those who did not. Similar results were demonstrated in comparable studies from Italy and Germany, which used claims data, focused on the older general population and applied methods of survival analysis [6, 7]. The distribution of drug classes from the PIM list showed that anxiolytics, hypnotics and sedatives were among the most frequently prescribed drug classes in the study. The most frequently prescribed PIM drug classes are presented in table S14 in the appendix. Thus, it seems plausible that medications from these drug classes have contributed to the positive association, as they are strongly associated with falls and cognitive impairment [41, 42], which can lead to severe adverse outcomes requiring hospital care. In addition, we found decreasing HRs over time based on the step function, indicating that severe adverse events requiring hospitalisation may occur shortly after exposure. This is in line with the results of a study that examined the temporal pattern of adverse events following drug administration, demonstrating that such events often occur within a short timeframe after exposure [43]. Furthermore, we explicitly included only patients without PIM exposure prior to the initial prescription. We assume that these patients responded more sensitively to initial PIM use and experienced immediate adverse effects as they had not developed medication tolerance or received regular re-assessment of their medication regimen to optimise care.

To the best of our knowledge, this is the first study in Switzerland to examine the differences in healthcare costs of the general older population with and without PIM prescription. Our findings revealed significantly higher healthcare costs in patients exposed to PIMs after adjustment for differences in sociodemographics and morbidity.

The cost differences were higher but in range with estimates of a systematic review [14], which evaluated the associated costs of PIMs in the general older population, and are likely to be explained by the different healthcare settings and methodologies applied. Considering that a large proportion of the older population was prescribed PIMs in Switzerland, our findings illustrate the significant financial burden of PIMs on the healthcare system. This might also strain healthcare resources and potentially affect quality and efficiency of healthcare, particularly in the context of skilled labour shortages and high clinician workloads.

Overall, the present study provides current estimates of PIM exposure and its associated risk of hospitalisation and healthcare costs in the general older population in Switzerland. Up-to-date and population-based data are crucial in the context of increasing political discussion on drug safety and healthcare costs in the older population. Assessments and evaluations of the extent of

the public health burden help healthcare providers and policymakers and enable evidence-based discussions and decision-making. Given the high PIM prevalence and the associated public health burden, there is an urgent need to reduce PIMs in the general older population in Switzerland. In line with prior research [44], our analysis showed that a small number of drug classes such as anxiolytics, hypnotics and sedatives account for the majority of PIM prescriptions and are likely to contribute to the observed associations. The findings may reflect a lack of awareness in prescribing PIMs in primary care and the challenge of managing conflicting treatment recommendations in vulnerable patients, where a careful balance of benefits and risks is essential. Future research should examine prescribing processes in these clinical contexts and identify approaches that effectively and efficiently minimise PIMs. While some PIMs might be unavoidable due to lack of alternative treatments for disease progression or pain management, even a modest reduction in PIMs is likely to improve patient outcomes and lower healthcare costs.

Strengths and limitations

The study has several strengths and limitations. First, the main strength of the study is the use of a large health insurance claims dataset which is practice-based and a reliable source of patient-level information. It provided comprehensive and per se unbiased information on the prescribed drug and healthcare services received by a large cohort of older adults with and without PIM prescription. The detailed data allowed us to identify the exact date of the initial PIM prescription and the subsequent hospitalisation. Second, the applied methodological approach including PSM followed by a multivariate adjusted regression analysis allowed robust estimators and reduced bias from potential confounders. Third, we applied a step function to model time dependence. This approach allowed the risk of hospitalisation to change at different time intervals and provided a more comprehensive and dynamic understanding of the temporal pattern of the association between the PIM and the risk of hospitalisation.

The study has also limitations.

First, the applied study design and dataset do not allow for any causal interpretation of the estimated results. Despite applying appropriate statistical methods and a washout period to reduce confounding and improve robustness, we cannot fully exclude the presence of unmeasured or unobserved confounding. Differences in underlying indications, multimorbidity and associated treatment needs between patients with and without PIMs exist and partly account for the observed higher hospitalisation and healthcare costs. The findings should therefore be interpreted as associations, and not as direct causal effects.

Second, our findings may not be fully generalisable to the entire older population of Switzerland due to selection bias. However, basic health insurance is mandatory in Switzerland, and Helsana Group is one of the largest insurers with a 16% market share and coverage across all geographical regions and age groups of Switzerland. While selection bias cannot be entirely excluded, we assume that it is unlikely to have substantial bias affecting our results.

Third, a comparison of patients with and without PIM exposure may not fully reflect the clinical reality. Patients at risk of PIM exposure may have been prescribed alternative medications classified as safer options, which reduce the risk of adverse effects while still providing therapeutic benefits. In some clinical situations, prescription of PIMs is unavoidable especially in severe or progressive diseases, which are more likely to occur in our target population of older adults. Nevertheless, using non-exposed patients as controls offers a suitable reference. PIM criteria focus primarily on identifying PIMs rather than providing alternatives; therefore comprehensive lists of alternative medications are not always available and might vary depending on the criteria used.

Fourth, the estimated CPH model does not account for PIM exposures that occurred between the initial prescription and subsequent hospitalisation. Therefore, we cannot exclude the potential influence of additional PIM prescription on the risk of hospitalisation. In fact, among exposed patients, those who were hospitalised were more likely to experience multiple PIM exposures within one year after the index date (55%) compared to non-hospitalised patients (44%). However, the primary aim in our study was to evaluate the impact of the initial PIM exposure, which is often the most clinically relevant one, as it represents the decision point where the risk is introduced.

Fifth, we cannot completely exclude the possibility of selection bias, which might also be reflected in changes in PIM prevalence within our outcome study sample resulting from the exclusion criteria applied during the washout and/or follow-up periods. However, we faced a trade-off between a clean study design that accounted for potential confounding factors related to earlier or later health issues and utilising a more complete and therefore more representative sample.

Sixth, the identification of PIMs and their associations with outcomes may vary depending on the PIM list applied [44]. In this study we used two well-established (Beers and PRISCUS) and widely adopted (Beers) lists. Furthermore, a recent study examining the prevalence of PIMs across multiple PIM lists found that only a few drug classes account for most prescriptions [44], and these classes are covered by the lists used in our analysis.

Lastly, we cannot entirely exclude the potential influence of the COVID-19 pandemic (2020–2021) on the outcomes in our study. However, we assume that the influence is limited as patients with chronic disease, which are highly prevalent in older populations, continued to receive necessary care [45].

Conclusion

This study showed a high PIM prevalence and associated public health burden in terms of hospitalisations and healthcare costs in the general older population of Switzerland. Our findings may indicate limited awareness in prescribing PIMs in primary care and the challenge associated with managing conflicting therapeutic recommendations in vulnerable patients. Given the ageing population and rising healthcare costs, the study highlights the urgent need for targeted strategies to reduce PIMs such as computer- and database-driven interventions for healthcare providers to efficiently detect and reduce PIMs.

Data sharing statement

The analysed dataset is not publicly available. The insurance claims data from Helsana Group are subject to protection and privacy restrictions and were used under licence for this study. Additional information is available from Helsana upon reasonable request.

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Potential competing interests .
All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Table S1. Drug classes including PIMs based on Beer's criteria and PRISCUS list

Table S2. Proportional hazard assumption test

Figure S3. Graphical analysis of proportional hazard assumption for PIM

Table S4. PIM Prevalence from 2012 to 2022

Figure S5. Absolute standardized mean difference

Table S6. Variance ratios

Figure S7. Density distributions of each variable

Figure S8. Density distributions of propensity scores before and after matching

Table S9. Patient characteristics of the study population before propensity score matching

Table S10. Estimated association between PIM prescription and hospitalization as well as healthcare costs excluding patients hospitalized within 15 days of follow-up

Table S11. Estimated association between PIM prescription and hospitalization as well as healthcare costs excluding patients 80 years and older 8

Table S12. Estimated association between PIM prescription and hospitalization as well as healthcare costs for distinct matches

Table S13. Estimated association between PIM prescription and healthcare costs using incident rate ratios

Table S14. Ten most frequently prescribed PIM drug classes

Table S1. Drug classes including PIMs based on Beer's criteria and PRISCUS list

26 Drug Classes
Sedatives/ Antipsychotics
Systemic Antihistamines
Anti-inflammatory and Antirheumatic Agents
Antidepressants / CNS Stimulants
Muscle Relaxants
Antihypertensive Agents
Analgesics
Cardiac Therapeutics
Topical Analgesics / Anti-inflammatory Agents
Sex Hormones and Genital System Modulators
Urological Agents
Beta-Adrenergic Blockers
Peripheral Vasodilators
Antithrombotic Agents
Anti-Parkinson Agents
Antiepileptic Drugs
Antidiabetic Agents
Systemic Antibacterials
Antipruritic Agents
Calcium Channel Blockers
Nasal Preparations
Other CNS Drugs
Anti-inflammatory and Antirheumatic Agents
Laxatives
Antiemetic and Antinauseant Agents
Drugs for Functional Gastrointestinal Disorders

Abbreviations: PIM, potentially inappropriate medications; CNS, central nervous system; ATC, Anatomical Therapeutic Chemical Classification System

Notes: Drug classes were reported at ATC-level 3. These classes aggregate multiple sublevels and may include substances that are not classified as PIMs.

Table S2. Proportional hazard assumption test

	x^2 (df)	p-value
PIM	53.000	0.000
Age	10.800	0.001
Female	0.006	0.939
Urban	1.030	0.311
Rural	0.612	0.434
DE	0.013	0.909
FR	0.767	0.381
FDM	0.001	0.974
FDM light	0.168	0.682
TM	0.461	0.497
Deductible	3.980	0.046
No. physicians (wo)	0.158	0.691
No. outp. cons (wo)	1.060	0.302
No. ATC (wo)	0.005	0.946
PCG 1-3 (wo)	0.188	0.665
PCG 4-5 (wo)	0.493	0.482
PCG ≥6 (wo)	0.279	0.597
Out. costs (wo)	0.000	0.999
Inp. costs (wo)	0.210	0.647
NH (wo)	0.733	0.392
GLOBAL	76.700	0.000

Abbreviation: x^2, Chi-square; df, degrees of freedom; PIM, potentially inappropriate medications; d, days; wo, washout; DE, German-speaking area; FR, French-speaking area; FDM, family doctor model; SCM, standard care model; TM, telemedicine model; No, number; outp., outpatient; inp. inpatient; ATC, Anatomical Therapeutic Chemical (classification system); PCG, pharmaceutical cost group; NH, nursing home stay

Figure S3. Graphical analysis of proportional hazard assumption for PIM

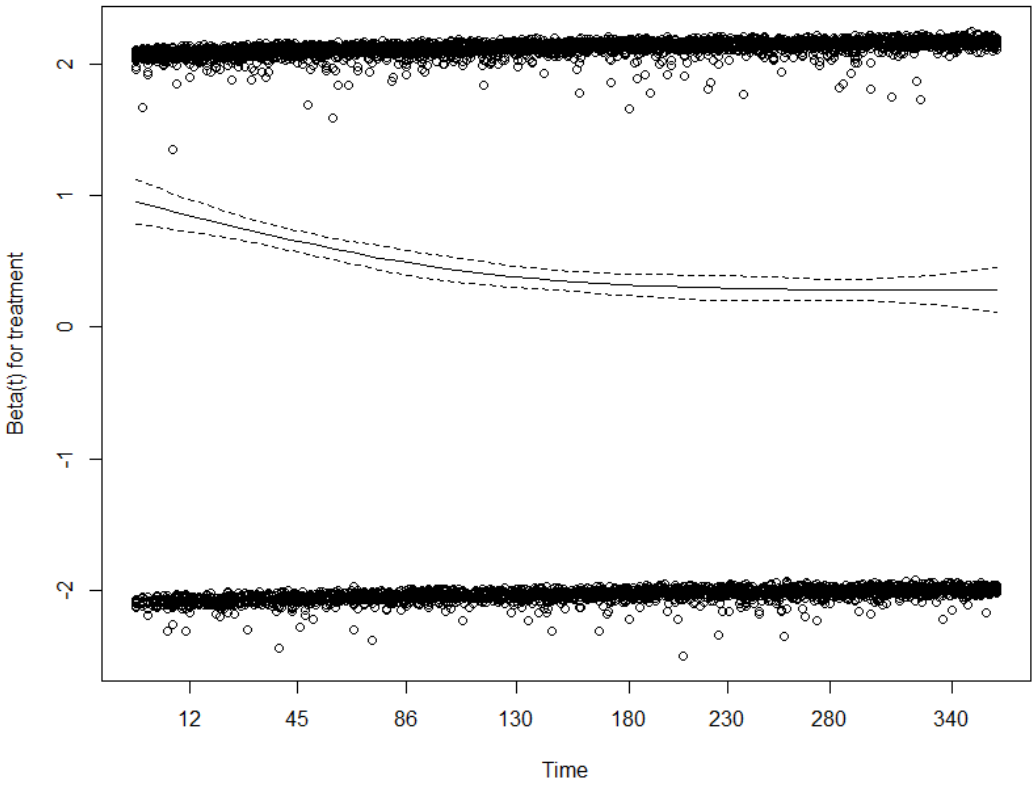

Table S4. PIM Prevalence from 2012 to 2022

Year	Total	N (%)
2012	251’486	93’712 (37.3)
2013	254’596	96’723 (38.0)
2014	256’624	97’915 (38.2)
2015	258’397	107’721 (41.7)
2016	257’293	104’571 (40.6)
2017	254’980	101’525 (39.8)
2018	257’169	100’398 (39.0)
2019	259’215	92’441 (35.7)
2020	264’627	90’460 (34.2)
2021	268’635	88’704 (33.0)
2022	272’058	88’879 (32.7)

Figure S5. Absolute standardized mean difference

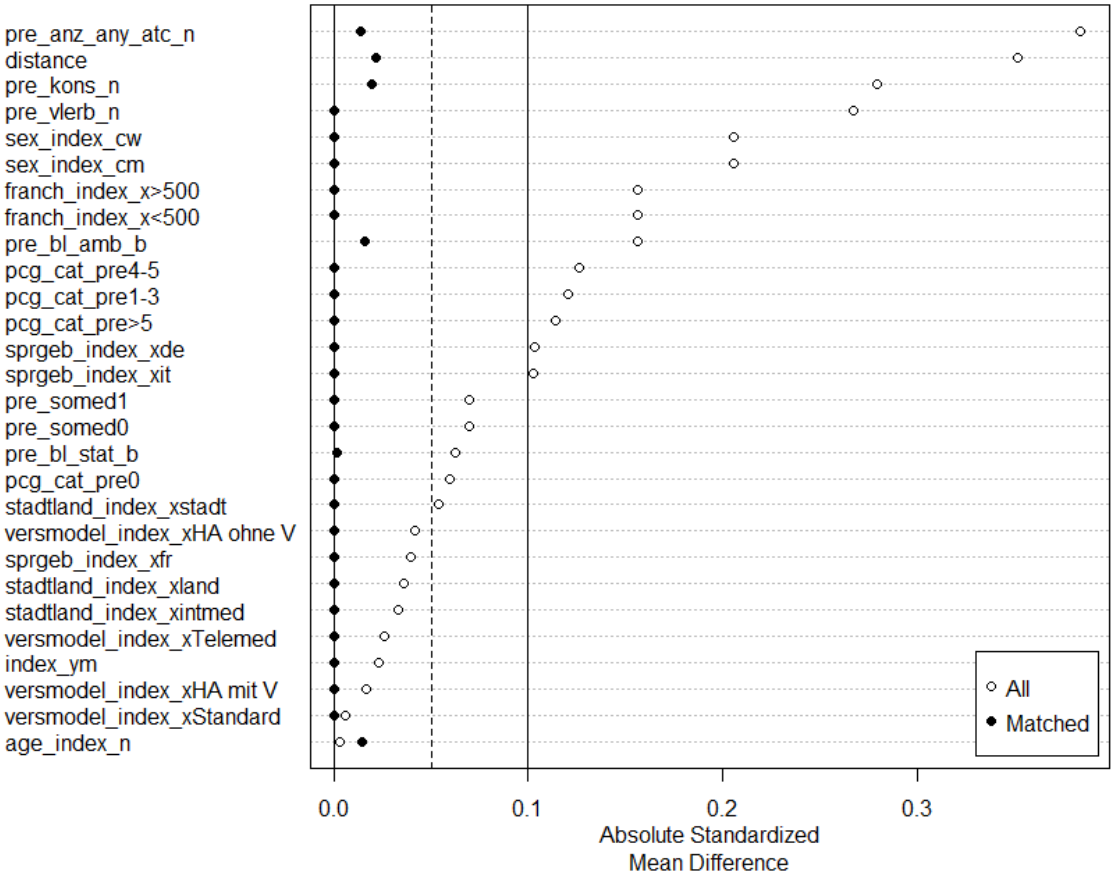

Table S6. Variance ratios

	All Data			Matched Data			
	Var. Ratio	**eCDF Mean**	**eCDF Max**	**Var. Ratio**	**eCDF Mean**	**eCDF Max**	**Std. Pair Dist.**
distance	2.50	0.14	0.20	1.26	0.00	0.00	0.04
index_ym	1.02	0.01	0.02	1.00	0.00	0.00	0.00
age_index_n	0.98	0.00	0.01	0.97	0.00	0.01	1.04
sex_index_cm		0.10	0.10		0.00	0.00	0.00
sex_index_cw		0.10	0.10		0.00	0.00	0.00
sprgeb_index_xde		0.04	0.04		0.00	0.00	0.00
sprgeb_index_xfr		0.01	0.01		0.00	0.00	0.00
sprgeb_index_xit		0.03	0.03		0.00	0.00	0.00
stadtland_index_xintmed		0.01	0.01		0.00	0.00	0.00
stadtland_index_xland		0.01	0.01		0.00	0.00	0.00
stadtland_index_xstadt		0.03	0.03		0.00	0.00	0.00
franch_index_x<500		0.05	0.05		0.00	0.00	0.00
franch_index_x>500		0.05	0.05		0.00	0.00	0.00
versmodel_index_xstandard		0.00	0.00		0.00	0.00	0.00
versmodel_index_xhamit v		0.01	0.01		0.00	0.00	0.00
versmodel_index_xhaohne v		0.01	0.01		0.00	0.00	0.00
versmodel_index_xtelemed		0.01	0.01		0.00	0.00	0.00
pre_anz_any_atc_n	1.44	0.04	0.18	1.04	0.00	0.01	0.27
pre_vlerb_n	1.37	0.02	0.11	1.03	0.00	0.01	0.76
pre_kons_n	1.44	0.01	0.15	0.88	0.00	0.01	0.63
pre_somed0		0.01	0.01		0.00	0.00	0.00
pre_somed1		0.01	0.01		0.00	0.00	0.00
pre_bl_amb_b	1.28	0.09	0.14	1.29	0.00	0.01	0.52
pre_bl_stat_b	1.61	0.01	0.02	1.02	0.00	0.00	0.13
pcg_cat_pre0		0.02	0.02		0.00	0.00	0.00
pcg_cat_pre1-3		0.06	0.06		0.00	0.00	0.00
pcg_cat_pre4-5		0.05	0.05		0.00	0.00	0.00
pcg_cat_pre>5		0.03	0.03		0.00	0.00	0.00

Abbreviation: eCDF, empirical Cumulative Distribution Function

Figure S7. Density distributions of each variable

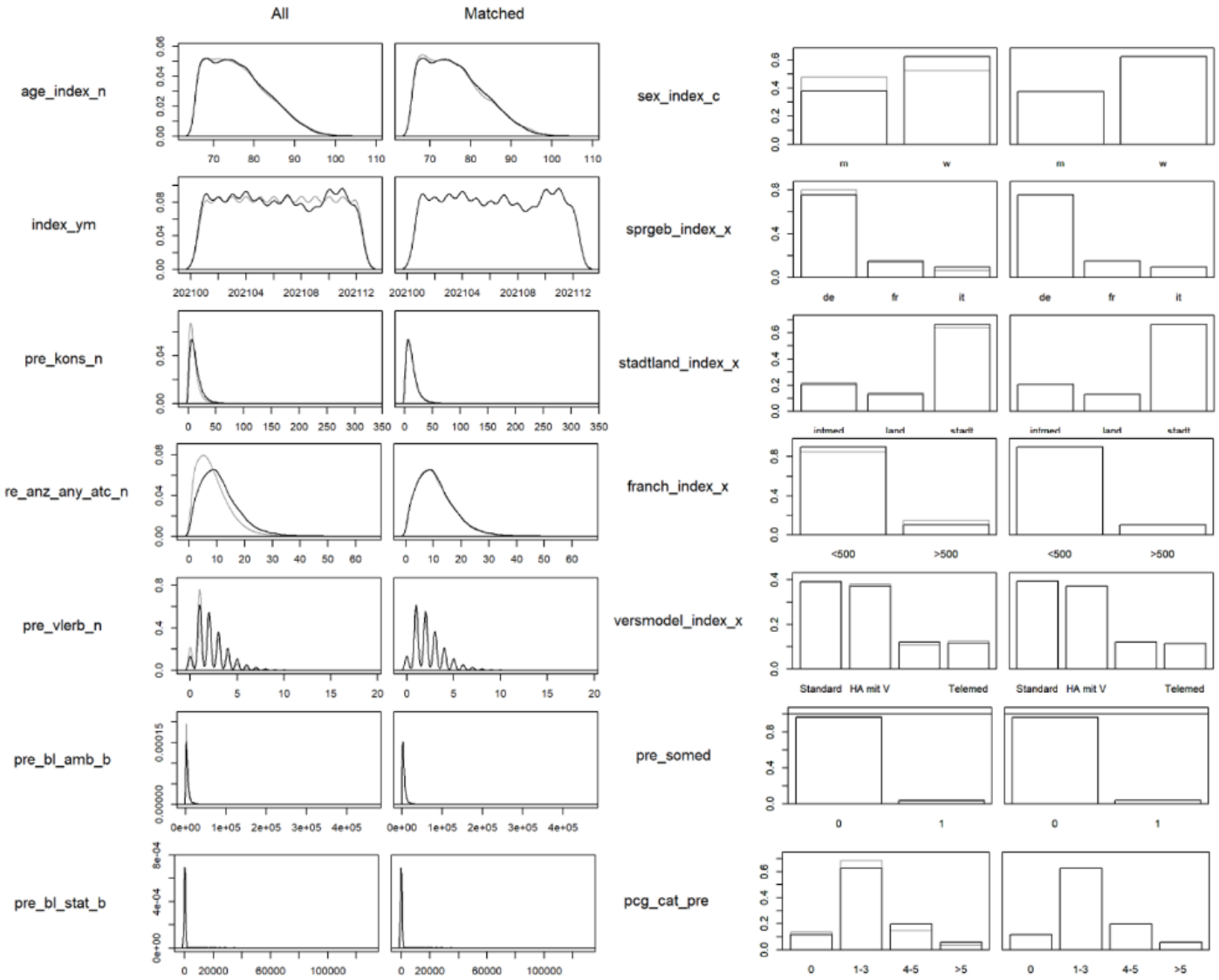

Figure S8. Density distributions of propensity scores before and after matching

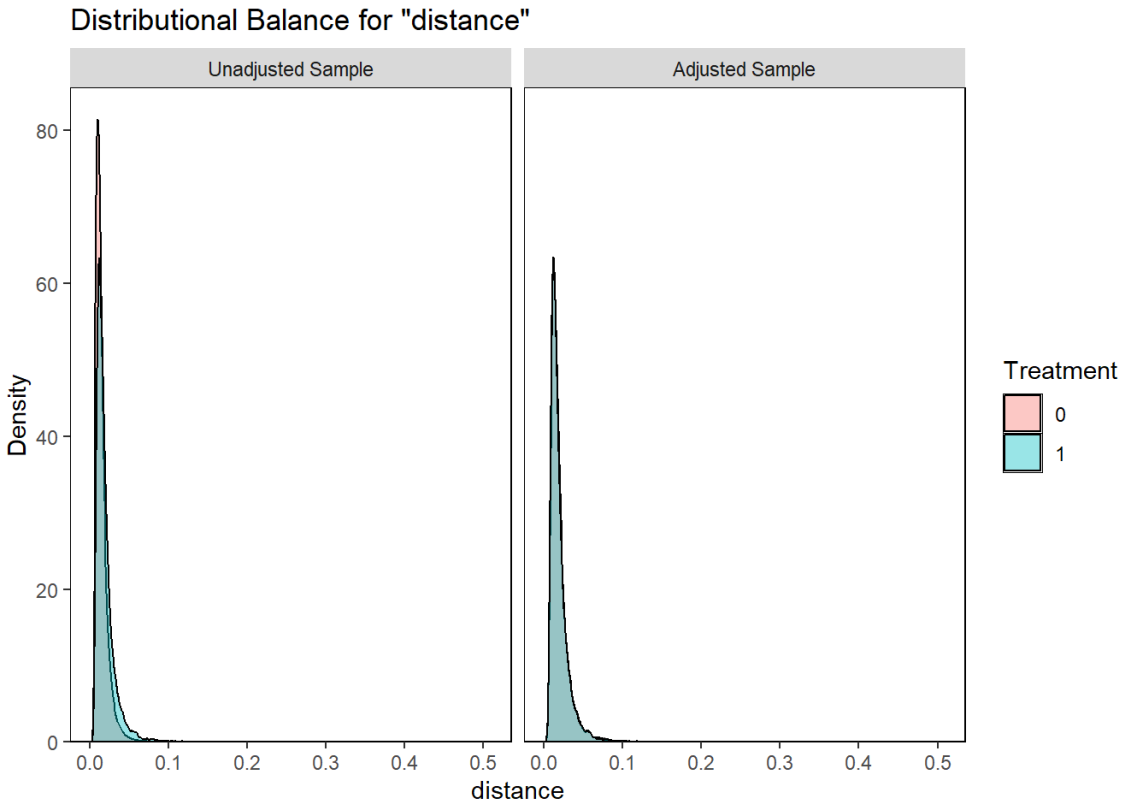

Table S9. Patient characteristics of the study population before propensity score matching

Sample	No PIM	PIM
	N (%)/ Mean (SD)	N (%)/ Mean (SD)
N	**1'159'138**	**17'738**
Demographics		
Sex (Female)	606'620 (52.3%)	11'049 (62.3%)
Mean age	76 (7.2)	76 (7.1)
Living area		
Urban	741'437 (64.0%)	11'800 (66.5%)
Rural	163'659 (14.1%)	2'290 (12.9%)
Intermediate	254'039 (21.9%)	3'648 (20.6%)
Language region		
German-speaking area	926'823 (80.0%)	13'396 (75.5%)
French-speaking area	156'767 (13.5%)	2'651 (14.9%)
Italian-speaking area	75'545 (6.5%)	1'691 (9.5%)
Health insurance model		
SCM	451'012 (38.9%)	6'953 (39.2%)
FDM	440'357 (38.0%)	6'594 (37.2%)
FDM-light	123'571 (10.7%)	2'132 (12.0%)
TM	144'195 (12.4%)	2'059 (11.6%)
Deductible (≤ CHF 500)	986'514 (85.1%)	15'935 (89.8%)
Number of chronic conditions (wo)		
0	156'507 (13.5%)	2'057 (11.6%)
1-3	793'352 (68.4%)	11'106 (62.6%)
4-5	171'488 (14.8%)	3'516 (19.8%)
≥6	37'782 (3.3%)	1'059 (6.0%)
Nursing home (wo)	32'826 (2.8%)	750 (4.2%)
N outpatient consultations (wo)	10 (10.1)	14 (12.0)
N diff. physicians (wo)	2 (1.4)	2 (1.6)
N. ATC (wo)	8 (5.6)	11 (6.7)
Costs CHF (wo)		
Outpatient costs	4'564 (7'410.3)	5'874 (8'378.1)
Inpatient costs	483 (3'329)	748 (4'224.7)

Abbreviations: N, number; SD, standard deviation; PIM, potentially inappropriate medication; SCM, standard care model; FDM, family doctor model; TM, telemedicine model; wo, washout; CHF, Swiss Francs

Notes: Washout refers to the period one year prior to the corresponding index date. Outpatient consultations include primary care and specialist physician. FDM: The treating physician is part of a physician network, which has a cooperation agreement with the health insurance, which defines reimbursement for integrated care services and regulates the type of cooperation and commit to a network-specific quality standard. FDM-Light: In contrast to FDM the treating physician is not part of an approved physician-network. Nursing home was defined as a ≥ 1 overnight stay.

Table S10. Estimated association between PIM prescription and hospitalization as well as healthcare costs excluding patients hospitalized within 15 days of follow-up

	All-cause Hospitalization aHR (CI)	p-value	Total healthcare costs ME (CI)	p-value
PIM				
PIM vs. no PIM			2'910.00 (2'766.00 to 3'054.00)	<0.001
PIM vs. no PIM: 30d	1.81 (1.48 to 2.20)	<0.001		
PIM vs. no PIM 60d	1.68 (1.44 to 197)	<0.001		
PIM vs. no PIM 90d	1.76 (1.49 to 2.07)	<0.001		
PIM vs. no PIM 180d	1.60 (1.45 to 1.76)	<0.001		
PIM vs. no PIM 365d	1.38 (1.29 to 1.49)	<0.001		
Covariates				
Age	1.02 (1.02 to 1.03)	<0.001	100.00 (89.00 to 110.00)	<0.001
Female vs. male	0.80 (0.76 to 0.84)	<0.001	-1'120.00 (-1'270.00 to -969.00)	<0.001
Intermedia vs. rural	0.92 (0.85 to 0.99)	0.08	-124.00 (-369.00 to -120.00)	0.32
Urban vs. rural	0.92 (0.82 to 1.02)	0.03	-134.00 (-347.00 to 79.00)	0.22
FR vs. IT	0.92 (0.82 to 1.02)	0.11	340.00 (40.00 to 639.00)	<0.05
DE vs. IT	1.10 (1.00 to 1.20)	0.04	107.00 (-139.00 to 353.00)	0.40
FDM vs. SCM	0.94 (0.89 to 1.00)	0.05	-291.00 (-450.00 to -132.00)	<0.001
FDM-light vs. SCM	0.95 (0.87 to 1.03)	0.24	-262.00 (-490.00 to -35.00)	<0.05
TM vs. SCM	0.93 (0.85 to 1.01)	0.08	-474.00 (-698.00 to -249)	<0.001
Deductible high vs. low	0.90 (0.82 to 0.99)	<0.05	-917.00 (-1'134.00 to -701.00)	<0.001
N. physicians (wo)	1.02 (1.00 to 1.04)	<0.05	134.00 (83.00 to 186.00)	<0.001
N. outp. Cons (wo)	1.00 (1.00 to1.00)	0.13	21.00 (13.00 to 29.00)	<0.001
N. ATC (wo)	1.03 (1.02 to 1.03)	<0.001	107.00 (91.00 to 124.00)	<0.001
PCG 1-3 (wo) vs. no PCG	1.05 (0.95 to 1.15)	0.36	921.00 (693.00 to 1'149.00)	<0.001
PCG 4-5 (wo) vs. no PCG	1.08 (0.96 to 1.21)	0.20	1'856.00 (1'509.00 to 2'203.00)	<0.001
PCG ≥ 6 (wo) vs. no PCG	1.14 (0.99 to 1.32)	0.07	2'069.00 (1'546.00 to 2'591.00)	<0.001
Outp. cost (wo)	1.00 (1.00 to 1.00)	<0.001	0.40 (0.39 to 0.42)	<0.001
Inp. cost (wo)	1.00 (1.00 to 1.00)	<0.05	0.26 (0.23 to 0.28)	<0.001
NH (wo) vs. no NH	0.67 (0.53 to 0.84)	<0.001	5'001.00 (4'058.00 to 5'945.00)	<0.001

Abbreviation: aHR, adjusted hazard ratio; ME, marginal effects; CI, confidence interval; PIM, potentially inappropriate medications; d, days; FR, French-speaking area; DE, German-speaking area; FDM, family doctor model; SCM, standard care model; TM, telemedicine model; wo, washout; N, number; pre, a year before index-date; outp., outpatient; inp. inpatient; ATC, Anatomical Therapeutic Chemical (Classification system); PCG, pharmaceutical cost group; NH, nursing home.

Notes: Sample sizes: 34'580 (17'290 matched pairs)

Table S11. Estimated association between PIM prescription and hospitalization as well as healthcare costs excluding patients 80 years and older

	All-cause Hospitalization aHR (CI)	p-value	Total healthcare costs ME (CI)	p-value
PIM				
PIM vs. no PIM			3'138 (2'979 to 3'297)	<0.001
PIM vs. no PIM: 15d	3.24 (2.55 to 4.12)	<0.001		
PIM vs. no PIM: 30d	2.26 (1.76 to 2.90)	<0.001		
PIM vs. no PIM 60d	1.75 (1.44 to 2.12)	<0.001		
PIM vs. no PIM 90d	2.00 (1.64 to 2.45)	<0.001		
PIM vs. no PIM 180d	1.59 (1.41 to 1.78)	<0.001		
PIM vs. no PIM 365d	1.34 (1.23 to 1.46)	<0.001		
Covariates				
Age	1.02 (1.02 to 1.03)	<0.001	85 (67 to 103)	<0.001
Female vs. male	0.77 (0.72 to 0.81)	<0.001	-1'154 (-1'317 to -991)	<0.001
Intermedia vs. rural	0.86 (0.78 to 0.95)	0.003	-458 (-715 to -201)	<0.001
Urban vs. rural	0.86 (0.79 to 0.93)	<0.001	-244 (-476 to -12)	0.039
FR vs. IT	0.90 (0.79 to 1.02)	0.089	393 (59 to 726)	0.021
DE vs. IT	1.12 (1.01 to 1.25)	0.033	163 (-110 to 437)	0.24
FDM vs. SCM	0.95 (0.89 to 1.02)	0.14	-75 (-252 to 102)	0.41
FDM-light vs. SCM	0.93 (0.84 to 1.02)	0.13	-289 (-539 to -39)	0.023
TM vs. SCM	1.00 (0.91 to 1.10)	0.97	-85 (-333 to 163)	0.50
Deductible high vs. low	0.99 (0.90 to 1.10)	0.89	-740 (-969 to -511)	<0.001
N. physicians (wo)	1.01 (1.0 to 1.03)	0.16	71 (15 to 128)	0.014
N. outp. Cons (wo)	1.00 (1.00 to 1.01	0.001	44 (35 to 53)	<0.001
N. ATC (wo)	1.03 (1.03 to 1.04)	<0.001	112 (94 to 131)	<0.001
PCG 1-3 (wo) vs. no PCG	0.97 (0.88 to 1.07)	0.54	751 (517 to 985)	<0.001
PCG 4-5 (wo) vs. no PCG	0.97 (0.85 to 1.09)	0.60	1'607 (1'235 to 1'979)	<0.001
PCG ≥ 6 (wo) vs. no PCG	0.93 (0.79 to 1.10)	0.42	1'611 (1'039 to 2'183)	<0.001
Outp. cost (wo)	1.00 (1.00 to 1.00)	<0.001	0.36 (0.34 to 0.37)	<0.001
Inp. cost (wo)	1.00 (1.00 to 1.00)	0.077	0.21 (0.17 to 0.26)	<0.001
NH (wo) vs. no NH	1.34 (0.90 to 2.01)	0.15	7'252 (4'973 to 9'531)	<0.001

Abbreviation: aHR, adjusted hazard ratio; ME, marginal effects; CI, confidence interval; PIM, potentially inappropriate medications; d, days; FR, French-speaking area; DE, German-speaking area; FDM, family doctor model; SCM, standard care model; TM, telemedicine model; wo, washout; N, number; pre, a year before index-date; outp., outpatient; inp. inpatient; ATC, Anatomical Therapeutic Chemical (Classification system); PCG, pharmaceutical cost group; NH, nursing home.

Notes: Sample sizes: 25'868 (12'934 matched pairs)

Table S12. Estimated association between PIM prescription and hospitalization as well as healthcare costs for distinct matches

	All-cause Hospitalization		Total healthcare costs	
	aHR (CI)	p-value	ME (CI)	p-value
PIM				
PIM vs. no PIM			3'163.00 (3'010.00 to 3'317.00)	<0.001
PIM vs. no PIM: 15d	2.58 (2.13 to 3.13)	<0.001		
PIM vs. no PIM: 30d	1.98 (1.60 to 2.46)	<0.001		
PIM vs. no PIM 60d	1.67 (1.42 to 1.96)	<0.001		
PIM vs. no PIM 90d	1.67 (1.41 to 1.98)	<0.001		
PIM vs. no PIM 180d	1.48 (1.34 to 1.63)	<0.001		
PIM vs. no PIM 365d	1.35 (1.25 to 1.45)	<0.001		
Covariates				
Age	1.02 (1.02 to 1.03)	<0.001	104.00 (93.00 to 115.00)	<0.001
Female vs. male	0.81 (0.77 to 0.86)	<0.001	-914.00 (-1'071.00 to -756.00)	<0.001
Intermedia vs. rural	0.98 (0.90 to 1.07)	0.67	-148.00 (-407.00 to -110.00)	0.26
Urban vs. rural	0.95 (0.88 to 1.03)	0.22	-88.60 (-314.00 to -137.00)	0.44
FR vs. IT	0.99 (0.89 to 1.10)	0.80	561.00 (232.00 to 889.00)	<0.001
DE vs. IT	1.14 (1.04 to 1.25)	<0.05	152.00 (-113.00 to 417.00)	0.26
FDM vs. SCM	0.98 (0.92 to 1.03)	0.43	-265.00 (-434.00 to -97.00)	<0.001
FDM-light vs. SCM	0.97 (0.89 to 1.05)	0.43	-198.00 (-442.00 to -46.00)	0.11
TM vs. SCM	0.99 (0.90 to 1.07)	0.74	-246.00 (-491.00 to -1.70)	0.05
Deductible high vs. low	0.95 (0.87 to 1.04)	0.26	-776.00 (-1'006.00 to -545.00)	<0.001
N. physicians (wo)	1.02 (1.01 to 1.04)	<0.05	131.00 (75.50 to 187.00)	<0.001
N. outp. Cons (wo)	1.00 (1.00 to 1.00)	<0.05	28.20 (20.00 to 37.00)	<0.001
N. ATC (wo)	1.03 (1.02 to 1.03)	<0.001	118.00 (136.00 to 100.00)	<0.001
PCG 1-3 (wo) vs. no PCG	1.04 (0.94 to 1.14)	0.46	842.00 (601.00 to 1'083.00)	<0.001
PCG 4-5 (wo) vs. no PCG	1.05 (0.94 to 1.18)	0.38	1'702.00 (1'337.00 to 2'066.00)	<0.001
PCG ≥ 6 (wo) vs. no PCG	1.12 (0.97 to 1.29)	0.13	1'811.00 (1'266.00 to 2'357.00)	<0.001
Outp. cost (wo)	1.00 (1.00 to 1.00)	<0.001	0.41 (0.39 to 0.42)	<0.001
Inp. cost (wo)	1.00 (1.00 to 1.00)	<0.05	0.25 (0.22 to 0.28)	<0.001
NH (wo) vs. no NH	0.68 (0.54 to 0.86)	<0.05	5'128 (4'126.00 to 6'129.00)	<0.001

Abbreviation: aHR, adjusted hazard ratio; ME, marginal effects; CI, confidence interval; PIM, potentially inappropriate medications; d, days; FR, French-speaking area; DE, German-speaking area; FDM, family doctor model; SCM, standard care model; TM, telemedicine model; wo, washout; N, number; pre, a year before index-date; outp., outpatient; inp. inpatient; ATC, Anatomical Therapeutic Chemical (Classification system); PCG, pharmaceutical cost group; NH, nursing home.

Notes: Sample sizes: 32'278 (16'139 matched distinct pairs)

Table S13. Estimated association between PIM prescription and healthcare costs using incident rate ratios

	Total healthcare costs aIRR (CI)	p-value
PIM		
PIM vs. no PIM	1.49 (1.46 to 1.51)	<0.001
Covariates		
Age	1.01 (1.01 to 1.01)	<0.001
Female vs. male	0.89 (0.87 to 0.91)	<0.001
Intermedia vs. rural	0.98 (0.95 to 1.01)	0.19
Urban vs. rural	0.99 (0.96 to 1.02)	0.41
FR vs. IT	1.06 (1.02 to 1.1)	<0.001
DE vs. IT	1.01 (0.98 to 1.04)	0.52
FDM vs. SCM	0.97 (0.95 to 0.99)	<0.001
FDM-light vs. SCM	0.97 (0.95 to 1)	0.07
TM vs. SCM	0.96 (0.93 to 0.99)	<0.05
Deductible high vs. low	0.91 (0.88 to 0.94)	<0.001
N. physicians (wo)	1.02 (1.01 to 1.02)	<0.001
N. outp. Cons (wo)	1.00 (1.00 to 1.00)	<0.001
N. ATC (wo)	1.01 (1.01 to 1.02)	<0.001
PCG 1-3 (wo) vs. no PCG	1.11 (1.08 to 1.14)	<0.001
PCG 4-5 (wo) vs. no PCG	1.23 (1.18 to 1.28)	<0.001
PCG ≥ 6 (wo) vs. no PCG	1.23 (1.17 to 1.3)	<0.001
Outp. cost (wo)	1.00 (1.00 to 1.00)	<0.001
Inp. cost (wo)	1.00 (1.00 to 1.00)	<0.001
NH (wo) vs. no NH	1.66 (1.54 to 1.79)	<0.001

Abbreviation: aIRR, adjusted incident rate ratio; CI, confidence interval; PIM, potentially inappropriate medications; d, days; FR, French-speaking area; DE, German-speaking area; FDM, family doctor model; SCM, standard care model; TM, telemedicine model; wo, washout; N, number; pre, a year before index-date; outp., outpatient; inp. inpatient; ATC, Anatomical Therapeutic Chemical (Classification system); PCG, pharmaceutical cost group; NH, nursing home.

Notes: Sample sizes: 35'400 (17'700 matched pairs)

Table S14. Ten most frequently prescribed PIM drug classes

Drug class	ATC	N (%)
Anxiolytics	N05B	80’337 (37.6%)
Hypnotics and sedatives	N05C	59’085 (27.7%)
Non-Steroidal Anti-Inflammatory Drugs	M01A	37’687 (17.6%)
Antidepressants	N06A	19’120 (9.0%)
Estrogens	G03C	13’902 (6.5%)
Laxatives	A06A	9’737 (4.6%)
Urological	G04B	5’100 (2.4%)
Progestogens and Estrogens in combination	G03F	4’981 (2.3%)
Antipsychotics	N05A	3’085 (1.4%)
Antihistamines for systemic use	R06A	2’973 (1.4%)

Abbreviations: N, number; ATC, Anatomical Therapeutic Chemical Classification System